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1: J Cell Biochem. 2001;82(4):591-8. Related Articles, Links

FULL TEXT AVAILABLE ONLINE at InterScience

Involvement of p38 MAP kinase in TGF-beta-stimulated VEGF synthesis in aortic smooth muscle cells.

Yamamoto T, Kozawa O, Tanabe K, Akamatsu S, Matsuno H, Dohi S, Uematsu T.

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Although it is known that transforming growth factor (TGF)-beta induces vascular endothelial growth factor (VEGF) synthesis in vascular smooth muscle cells, the underlying mechanisms are still poorly understood. In the present study, we examined whether the mitogen-activated protein (MAP) kinase superfamily is involved in TGF-beta-stimulated VEGF synthesis in aortic smooth muscle A10 cells. TGF-beta stimulated the phosphorylation of p42/p44 MAP kinase and p38 MAP kinase, but not that of SAPK (stress-activated protein kinase)/JNK (c-Jun N-terminal kinase). The VEGF synthesis induced by TGF-beta was not affected by PD98059 or U0126, specific inhibitors of the upstream kinase that activates p42/p44 MAP kinase. We confirmed that PD98059 or U0126 did actually suppress the phosphorylation of p42/p44 MAP kinase by TGF-beta in our preparations. PD169316 and SB203580, specific inhibitors of p38 MAP kinase, significantly reduced the TGF-beta-stimulated synthesis of VEGF (each in a dose-dependent manner). PD169316 or SB203580 attenuated the TGF-beta-induced phosphorylation of p38 MAP kinase. These results strongly suggest that p38 MAP kinase plays a part in the pathway by which TGF-beta stimulates the synthesis of VEGF in aortic smooth muscle cells. Copyright 2001 Wiley-Liss, Inc.

PMID: 11500937 [PubMed - indexed for MEDLINE]

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1: Biochem Soc Trans. 2003 Dec;31(Pt 6):1171-7.
Transactions

Related Articles, Links

VEGF signalling: integration and multi-tasking in endothelial cell biology.

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The central role of VEGF (vascular endothelial growth factor A) in angiogenesis is dependent upon its ability to co-ordinately regulate multiple endothelial functions. The multifunctionality of VEGF at the cellular level results from its ability to initiate a diverse, complex and integrated network of signalling pathways via its major receptor, kinase-insert-domain-containing receptor (KDR). Activation of phospholipase C-gamma, protein kinase C, Ca(2+), ERK (extracellular-signal-regulated protein kinase), Akt, Src, focal adhesion kinase and calcineurin pathways has been implicated in mediating multiple VEGF functions, including survival, proliferation, migration, vascular permeability, tubulogenesis, NO and prostanoid synthesis, and gene expression. NO and prostanoids in turn play paracrine and autocrine roles in linking post-receptor signalling to biological functions. Integration between biologically important signalling cascades occurs at several points. Akt and ERK, for example, are key junction points linking together signal transduction involved in survival and NO generation, and proliferation and prostanoid biosynthesis. Together, the multiplicity, functional versatility and integration of VEGF signalling provide a useful framework for understanding the mechanisms underlying the endothelial biological response to this key factor.

Publication Types:
- Review

MeSH Terms:
- Animals
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- Endothelium, Vascular/cytology
- Endothelium, Vascular/metabolism*
- Neuropilins/metabolism
- Receptors, Vascular Endothelial Growth Factor/metabolism
- Research Support, Non-U.S. Gov't
- Signal Transduction*
- Vascular Endothelial Growth Factor A/metabolism*

Substances:
- Neuropilins
- Vascular Endothelial Growth Factor A

- Receptors, Vascular Endothelial Growth Factor

PMID: 14641020 [PubMed - indexed for MEDLINE]

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1: Cardiovasc Res. 2006 Feb 1;69(2):512-9. Epub 2005 Dec 5. Related Articles, Links

ELSEVIER FULL-TEXT ARTICLE

Involvement of COX-2 in VEGF-induced angiogenesis via P38 and JNK pathways in vascular endothelial cells.

Wu G, Luo J, Rana JS, Laham R, Sellke FW, Li J.

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OBJECTIVE: Cyclooxygenase-2 (COX-2) is induced by hypoxic stimuli and is also involved in the process of angiogenesis. We previously demonstrated that vascular endothelial growth factor (VEGF) is one of the principal factors produced by hypoxic myocytes and is responsible for the induction of COX-2 expression in endothelial cells. Yet the signaling pathways by which VEGF modulates COX-2 gene expression are still less well defined. We therefore examined the regulation of VEGF-induced COX-2 expression by the mitogen-activated protein kinase (MAPK) family in endothelial cells. METHODS AND RESULTS: Human umbilical vascular endothelial cells (HUVECs) were incubated with U0126 (ERK1/2 inhibitor, 10 microM), SB203580 (p38 inhibitor, 20 microM), and SP600125 (JNK inhibitor, 20 microM), as well as the COX-2 selective inhibitor, NS398, for 1 h before treating with VEGF (20 ng/ml). COX-2 expression induced by VEGF at both mRNA and protein levels was significantly inhibited by selective p38 and JNK inhibitors but not by the ERK1/2 inhibitor. The phosphorylation of p38 and JNK kinases was observed as early as 5 min in HUVECs after VEGF stimulation. Furthermore, the biological significance of the COX-2 gene in endothelial cells was examined by over-expressing or knocking down COX-2 gene expression. (3)H-Thymidine incorporation and Matrigel techniques were used to determine cell proliferation and vascular structure formation. VEGF-induced cell proliferation was significantly reduced when HUVECs were either pre-treated with NS398 (21.52+/-3.6%) or transfected with COX-2 siRNA (34.12+/-5.81%). In contrast, in HUVECs with over-expression of COX-2, VEGF-induced cell proliferation was increased 42.56+/-7.69%. Moreover, the formation of vascular structure assayed by Matrigel demonstrated that VEGF-induced vascular structure formation was accelerated in COX-2 over-expressing cells but attenuated in COX-2 siRNA-transfected cells. CONCLUSION: COX-2 plays an important role in VEGF-induced angiogenesis via p38 and JNK kinase activation pathways. These findings suggest that the cardioprotective role of COX-2 may be, at least in part, through its angiogenic activity.

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0193-1849/03 $5.00
Vol. 284, Issue 6, E1202-E1209, June 2003

p38 MAP kinase regulates BMP-4-stimulated VEGF synthesis via p70 S6 kinase in osteoblasts

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We previously reported that p70 S6 kinase takes part in bone morphogenetic protein-4 (BMP-4)-stimulated vascular endothelial growth factor (VEGF) synthesis in osteoblast-like MC3T3-E1 cells. Recently, we showed that BMP-4-induced osteocalcin synthesis is regulated by p44/p42 MAP kinase and p38 MAP kinase in these cells. In the present study, we investigated whether the MAP kinases are involved in the BMP-4-stimulated synthesis of VEGF in MC3T3-E1 cells. PD-98059 and U-0126, inhibitors of the upstream kinase of p44/p42 MAP kinase, failed to affect BMP-4-stimulated VEGF synthesis. SB-203580 and PD-169316, inhibitors of p38 MAP kinase, significantly reduced VEGF synthesis, whereas SB-202474, a negative control for p38 MAP kinase inhibitor, had little effect on VEGF synthesis. The BMP-4-stimulated phosphorylation of p38 MAP kinase was not affected by rapamycin, an inhibitor of p70 S6 kinase. On the contrary, SB-203580 and PD-169316 reduced the BMP-4-stimulated phosphorylation of p70 S6 kinase. In addition, anisomycin, an activator of p38 MAP kinase, phosphorylates p70 S6 kinase, and the phosphorylation was suppressed by SB-203580. LY-294002, an inhibitor of phosphatidylinositol 3-kinase, failed to suppress the phosphorylation of p38 MAP kinase induced by BMP-4. Not BMP-4 but anisomycin weakly induced the phosphorylation of phosphoinositide-dependent kinase-1. However, anisomycin had little effect on phosphorylation of either Akt or the mammalian target of rapamycin. Taken together, our results suggest that p38 MAP kinase functions in BMP-4-stimulated VEGF synthesis as a positive regulator at a point upstream from p70 S6 kinase in osteoblasts.

bone-morphogenetic protein; vascular endothelial growth factor; mitogen-activated protein kinase; osteoblast